Re-evaluation Note REV2008-03

Review of the 2004 Re-evaluation of Citronella Oil and Related Active Compounds for Use as Personal Insect Repellents

In September 2004, Health Canada's Pest Management Regulatory Agency (PMRA) proposed to phase out registrations for personal insect repellents containing citronella oil and related active compounds unless registrants provided data to address uncertainties identified during the re-evaluation. The rationale for this proposal was published for consultation in Proposed Acceptability for Continuing Registration document PACR2004-36, *Re-evaluation of Citronella Oil and Related Active Compounds for Use as Personal Insect Repellents*.

To address the differences between the outcome of the PMRA's standard risk assessment and the perceived safety of citronella oil, the PMRA convened an independent scientific panel in November 2005 to review the basis for the proposed decision in PACR2004-36.

This document provides a summary of the scientific panel's review and recommendations, the PMRA's response and a revised qualitative health risk assessment for insect repellents containing citronella oil.

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1.0 Introduction

The PMRA published PACR2004-36, *Re-evaluation of Citronella Oil and Related Active Compounds for Use as Personal Insect Repellents*, on 17 September 2004. The PMRA recommended that citronella-based insect repellents that are applied to the skin be phased out unless further data are provided to address data uncertainties and endpoints of concern. The comment phase ended 17 November 2004. Minor comments were received and registrants did not commit to generating the data required to address the uncertainties identified during the re-evaluation.

In response to concerns expressed about the PMRA's proposed decision, the PMRA published Re-evaluation Note REV2005-05, Update on the Re-evaluation of Citronella Oil and Related Active Compounds for Use as Personal Insect Repellents (17 June 2005), which announced the PMRA's intention to convene an independent scientific panel to review the basis for the decision proposed in PACR2004-36 prior to finalizing its decision. The joint Citronella Review Panel-PMRA meeting was held 23 November 2005. The final *Report of an Independent Science Panel on Citronella Oil Used as an Insect Repellent* was received 23 March 2006.

The PMRA has considered the Panel's recommendations. This document outlines the PMRA's responses to the Panels recommendations. The PMRA has revised its health risk assessment based on the recommendations of the Panel. The revised health risk assessment is appended to this document. It must be noted that due to limitations in the data available, the revised health risk assessment is qualitative in nature.

2.0 Regulatory Status in Other Countries

As a result of re-evaluation activities in the European Union, data was requested to support the continued registration of citronella containing products, with a deadline of 1 September 2006. The citronella industry declined to provide the requested data and, therefore, all registrations in the European Union were cancelled as of 1 September 2006.

In the United States, a Reregistration Eligibility Decision document is available for citronella oil. The decision was based on an assessment of mutagenicity and acute toxicity. Citronella is currently listed under the *Federal Insecticide, Fungicide, and Rodenticide Act*, section 25(b), as exempt from normal registration requirements if a list of conditions are met.

3.0 Panel Recommendations and the PMRA's Response

The following text includes the questions put to the Panel, the Panel's recommendations with respect to each question and the PMRA's response to the recommendations. In some cases, the Panel chose to merge two or more questions in providing recommendations. Where this has occurred, the PMRA has provided a response to the merged recommendation.

Hazard Assessment: General Approach

Question 1
Does the Panel concur with the component-based hazard assessment approach taken by the PMRA?

Summarized Panel Response and Recommendations
"Therefore, the Panel agrees with the PMRA that the component based approach is the best way to evaluate citronella oil."

Summarized Recommendations
The safety evaluation procedures outlined in Monroe and Mattia (2004) and Smith et al. (2005) should be followed.

"Further safety data should be acquired from the literature on major components of citronella oil."

"The PMRA needs to develop identity and quality criteria for this product." "Consult with Natural Health Products Directorate (NHPD) which has experience with essential oils."

"The Panel recommends that methyleugenol concentrations be controlled to undetectable levels or that a risk based standard for methyleugenol in the oil be set by the PMRA on the basis of the methyleugenol National Toxicology Program (NTP) study."

PMRA Response
The PMRA is in agreement with the Panel that a component-based approach is the most appropriate method of assessment for the safety of citronella oil and related active ingredients in the absence of appropriate direct safety data for citronella oil.

The PMRA applied the Panel-recommended procedures to the safety assessment of citronella oil; see Appendix I of this document for details. Application of the assessment process outlined by Monroe and Mattia (2004) and Smith et al. (2005) did not alter the proposed regulatory decision outlined in PACR2004-36. The continued registration of citronella oil is not supported based on currently available scientific data. In support of the new assessment process, the PMRA sought additional information on the components of citronella oil from the scientific literature. However, little additional or applicable data were located.

Monroe and Mattia (2004) and Smith et al. (2005), in addition to a procedure for safety evaluation of natural flavour complexes (NFC; also known as essential oils), also proposed specification requirements which supported the safety evaluation process they described. The chemical specifications to describe an NFC suggested by these authors attempt to tie the chemical composition of an NFC more closely to the safety evaluation procedure they outline. The suggested specifications are largely compatible with those currently used by the PMRA. Key considerations in the proposed specifications include:

a) source information (plant, geographic location, degree of maturity, plant part used, method of isolation and any further processing);
b) ± 95% of the constituents of the NFC identified;
c) specify upper limits of concentrations for congeneric groups; and
d) provide information on trace constituents or levels of unidentified constituents that may be of a safety concern at sufficiently high concentrations (i.e. methyl eugenol).

Monroe and Mattia (2004) provided example specifications. However, identifying congeneric groups for constituents is difficult. At one time, the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the Flavour and Extract Manufacturers Association (FEMA), and the Research Institute for Fragrance Materials (RIFM) had agreed to use a single common table of groups to which individual constituents were assigned. JECFA has since subdivided many of these groups, but has not published a revised table identifying these groups or a total listing of chemicals in the various groups. In addition, individual constituents may change, and have changed groups over time as new information and safety reviews are generated. Until this issue is resolved, it will be difficult to implement all elements of the suggested specifications.

Applicable NHPD guidance concerning specifications related to essential oils is contained in *Evidence for Quality of Finished Natural Health Products*, dated November 2003. This guidance is generally compatible with the requirements of the *Pest Control Products Act* and Regulations and suggested specification requirements by Monroe and Mattia (2004) and Smith et al. (2005). The Natural Health Products Regulations (Section 44) specifications for natural health products are reproduced below:

44.(1) Every natural health product available for sale shall comply with the specifications submitted in respect of that natural health product under paragraph 5(*l*) and with every change to those specifications made by the product licence holder.
(2) The specifications shall contain the following information:
  (a) detailed information respecting the purity of the natural health product, including statements indicating its purity tolerances;
  (b) for each medicinal ingredient of the natural health product, detailed information respecting its quantity per dosage unit and its identity, including statements indicating its quantity and identity tolerances;

(c) if a representation relating to the potency of a medicinal ingredient is to be shown on a label of the natural health product, detailed information respecting the potency of the medicinal ingredient including statements indicating its potency tolerances;

(d) a description of the methods used for testing or examining the natural health product.

(3) The specifications and every change to those specifications shall be approved by a quality assurance person.

The *Food and Drugs Act* and Regulations also does not make clear specifications that would aid in developing a new specification standard for these type of products. Food flavourings are evaluated on a case-by-case basis under the *Food and Drugs Act* and Regulations.

The PMRA agrees with the Panel's recommendation that the methyleugenol content of active ingredients be regulated. PACR2004-36, *Re-evaluation of Citronella Oil and Related Active Compounds for Use as Personal Insect Repellents*, did propose to regulate methyleugenol content based on the National Toxicology Program studies (1998) of methyleugenol. The PMRA had proposed adopting the risk assessment of the European Commission (2000, 2001), which provided specific limits for methyleugenol in cosmetic products, that were considered to be equivalent to personal insect repellent use.

Question 2
Can the Panel recommend other ways to refine the hazard assessment or suggest an alternative approach that may be more appropriate?

Summarized Panel Response and Recommendations
"Alternative methods for hazard assessment include methods specified in the regulations of the NHPD."

Summarized Recommendations
"...Citronella oil when used as an insect repellent appear to fit the traditional use criteria used for Natural Health Products (NHPs). Since citronella oil has been in use for 50 or more years as an insect repellent with few adverse reports in the literature, its use could be supported under this criterion after suitable review."

"....some adverse reactions have been reported for essential oils taken orally by young children, these products are restricted to older children and adult use." "As a precaution, it is recommended by this panel that a restriction for use on small children under six years of age be considered."

PMRA Response
The PMRA, supported by the Panel, considers the component-based approach to be the best method to assess the safety of natural oil products such as citronella in the absence of direct toxicity data on citronella oil. As indicated in the response to the Panel's recommendations for Question 1, the PMRA applied the recommended safety evaluation procedure to the safety assessment of citronella oil.

The Panel has recommended that the PMRA include 'safe history of use' as a criterion in the safety assessment for citronella-oil-based personal insect repellents, based on the safety assessment approach of the Natural Health Products Directorate (NHPD). The PMRA has reviewed the NHPD regulations and available guidance documents with respect to history of use information as part of a risk assessment.

In addition to the review of standard toxicity data, history of use information can be included as part of a weight-of-evidence approach in a pesticide regulatory decision. While the PMRA has not had an incident reporting system until recently, other countries have had such systems in place for some time. In general, recorded adverse effects related to insect repellent uses of citronella have consisted of skin irritation or allergic reactions. However, review of available toxicity data has identified potential reproductive and developmental toxicities of concern. Due to the type of toxic effect identified, the use conditions for insect repellents, and the low probability of individuals associating toxic effects with the use of products perceived as safe, the PMRA has a low level of confidence that toxic effects occurring in humans as a result of citronella insect repellent usage would be related through a history of use. Therefore, it was not considered appropriate to base a regulatory decision for insect repellent uses of citronella solely on its history of use. Within the context of a weight-of-evidence assessment of health risk, the history of use for citronella as an insect repellent was given less weight than the potential reproductive and developmental toxicities identified in the available toxicity data.

As the NHPD considers human clinical trial data to be of greatest value in determining the safety of a product, a literature search was conducted to locate any such data related to any medical claims associated with citronella oil. No clinical trial data was located for citronella oil. Some data was available for lemongrass oil; however, the composition of lemongrass oil, although a related grass to the source of citronella oil, is different than that of citronella oil.

Databases of human data such as the Natural Medicines Comprehensive Database were consulted for available information related to citronella oil. This database is commonly used by the NHPD as a source of information related to natural substances. The record available for citronella oil notes that citronella seems to be safe for most people when used dermally and appropriately, but was noted to be a skin sensitizer. It was noted as being unsafe orally in large amounts for adults or children. One toddler death was noted following ingestion of an insect repellent containing citronella. Due to a lack of reliable information, a recommendation was made to avoid using citronella during pregnancy and lactation. These findings were echoed in the database record for citronella oil available at Drugs.com.

The Panel has recommended that an age restriction be considered for products containing citronella oil based on poisoning incidents with other essential oils. Poisonings with clove oil, eucalyptus oil and camphorated oils are increasing in incidence and outcomes include death. These oils are available in a variety of strengths. The principle component of clove oil is eugenol (a constituent of citronella oil), with acute poisoning causing liver failure and brain damage. The increasing use of natural/botanical products and the availability of these products in relatively concentrated form have lead to an increasing incidence of poisonings. However, based on the acute toxicology profile of citronella oil and the concentrations available in currently registered formulated products, such poisonings are unlikely for the citronella-based insect repellents.

An age restriction currently exists on most, but not all, registered insect repellent products containing citronella oil. Currently, labels indicate that use on children under two is inappropriate based on the availability of barrier methods for insect protection (e.g. bug nets for child carriers and playpens, clothing). The age restriction can also accompany general instruction to avoid application to the hands or face of older children in order to minimize inadvertent oral exposure. These labelling measures can be standardized on all labels.

Hazard Assessment: Endpoint and Safety Factor Selection

Question 3
Based on the data available at the time of the review, does the Panel concur with the developmental toxicity endpoint selected for the acute and short-term risk assessments?

Summarized Panel Response and Recommendations
The Panel raised a number of concerns with the PMRA's use of the Araujo et al. (1996) study that examined the developmental toxicity assay of alpha-terpinene in rats. The concerns the Panel noted included the extent of variation in the data, accuracy of the statistical analysis, accuracy of the study as judged by the lack of dose response for specific observations and the method of quantification of effects on ossification in the fetus. The Panel concluded, based on these concerns, that the PMRA's use of the Araujo et al. (1996) study was not appropriate for inclusion in the hazard and risk assessment of citronella oil.

The Panel further suggested that the Toaff et al. (1979) study (single-dose dermal rat reproduction study for citral) was considered appropriate for use for hazard and risk assessment purposes. The Panel noted that the difference between rat and human dermal absorption potential should be considered in the risk assessment.

PMRA Response
The PMRA disagrees with the Panel's analysis of the Araujo et al. (1996) and Toaff et al. (1979) studies.

The Araujo et al. (1996) study is a published research report, and the raw data were not available for examination at the time of review. Concerns related to the statistical analysis cannot be addressed without individual animal data. The study design appears to have followed or included elements described in standard guideline protocols outlined by the United States Environmental Protection Agency and included standard statistical tests.

Study findings that did not demonstrate a dose-response relationship or were unlikely to be treatment related, such as the fetal findings of hematoma and kinky tail identified by the Panel, were not relied upon for determination of the no observed adverse effect level/lowest observed adverse effect level (NOAEL/LOAEL) values for the study. The fetal NOAEL of 30 mg/kg bw/day determined for this study was based on increased incidences of delayed ossification and increased incidence of minor skeletal abnormalities. The maternal NOAEL of 60 mg/kg bw/day

was based on decreased maternal body-weight gain. Of most concern to the PMRA, and an observation that affected the choice of safety/uncertainty factors applied to the fetal NOAEL, was the observation that effects were noted in the fetus below the dose that affected the maternal animals.

Examination of maternal weight gain during the dosing period (days 6–15) and maternal body-weight gain corrected for gravid uterine weight over the test period (days 0–20), clearly demonstrates a dose-related reduction in body-weight gain which reached statistical significance in the top two dose groups. Such a maternal effect is expected to have an effect on fetal parameters such as fetal body weight, as was observed in the high dose group. This effect in the top two dose groups was the basis for the maternal NOAEL of 60 mg/kg bw/day.

The Alizarin Red S technique used by Araujo et al. (1996) to examine fetuses for skeletal anomalies, including changes in ossification, is consistent with the PMRA's Good Laboratory Practice guidelines and international protocols for developmental toxicity studies. The assessment of ossification, although not categorized by severity in the summary table, clearly indicates a dose response at doses of ≥60 mg/kg bw/day. The finding of delayed ossification is interpreted to represent a developmental delay which resolves in the postnatal period. A dose related increase in fetuses with one or more skeletal abnormalities was noted at doses ≥60 mg/kg bw/day. A statistically increased incidence of irregularly shaped os squamosum was noted at doses ≥60 mg/kg bw/day, with other skeletal structures affected at higher doses.

Although access to raw data would have been beneficial, the PMRA considers the study design and results of the Araujo et al. (1996) study acceptable and applicable to the hazard and risk assessment of citronella oil components in congeneric group 31.

The Toaff et al. (1979) study, although conducted by a more relevant route of exposure, did not follow a standard protocol for the conduct of the study either for dosing schedule or number of doses selected for testing. The study included only one dose level, which did not permit examining a dose-response or setting a NOAEL. The cause of death was not determined for the animals that died, making an association with dosing uncertain. These limitations place a large degree of uncertainty on the results thus making it difficult to rely upon the study to define regulatory decisions. The Panels recommendations with respect to dermal absorption are addressed below, in association with the Panel's and the PMRA's response to questions 5, 6 and 7.

It should also be noted that, following the safety evaluation procedures outlined in Monroe and Mattia (2004) and Smith et al. (2005), the Araujo et al. (1996) study is applicable to the hazard and risk assessment of congeneric group 31, while the Toaff et al. (1979) study is applicable to congeneric group 3. The Araujo et al. (1996) study provides the most sensitive indicator of potential toxicity among the available studies applicable to congeneric group 31. As such, it formed the basis for risk assessment for this congeneric group, consistent with normal regulatory practice. Due to the uncertainties present in the Toaff et al. (1979) study and the availability of other studies that defined NOAEL values at lower doses, the Toaff et al. (1979) study was not used for risk-assessment purposes in congeneric group 3.

Question 4
Does the Panel consider the safety factors selected for risk assessment to be appropriate with respect to human health protection?

Summarized Panel Response and Recommendations
"Since a component-based analysis of safety was chosen, it should have been based either on the major and/or the more toxic constituents."

"Minimally, given that the safety assessment of citronella oil conducted by the PMRA is based on a component toxicity assessment, chemical specific data should be acquired for at least one particular aspect of uncertainty (toxicokinetic differences between animals and humans for the compound under assessment) to replace the relevant part of the overall default uncertainty factor, as proposed by Dorne and Renwick (2005) and Dorne et al. (2005)."

"...the use of an additional 30-fold uncertainty factor is questionable."

PMRA Response
The Panel suggested that the PMRA's choice of citronella oil component for the 2004 risk assessment may not have been the most suitable. The procedures outlined by Monroe and Mattia (2004) and Smith et al. (2005) recommended by the Panel and implemented in the PMRA's revised risk assessment are a component based system that groups components of citronella oil based on structural and toxicological similarity (congeneric groups). Within each congeneric group, the most relevant and conservative toxicological endpoint is identified from the available toxicological data relevant to that group. Safety/uncertainty factors are determined for each of the congeneric groups and applied to the relevant toxicological endpoint. An acceptable margin of exposure is required all congeneric groups for citronella oil to achieve an acceptable margin of exposure. This procedure takes into account the relative proportions of citronella oil components and their toxicities.

The Panel recommended that the total applied safety/uncertainty factor the PMRA used in its 2004 assessment be refined by the generation of data and according to recommendations made by Dorne and Renwick (2005) and Dorne et al. (2005). The total safety factor that was originally applied was comprised of two components; a default 100-fold factor and an additional 30-fold factor necessary based on the database available for citronella oil. The PMRA has reconsidered available toxicity data and the application of uncertainty/safety factors in the context of the evaluation procedures outlined by Monroe and Mattia (2004) and Smith et al. (2005) for the health risk assessment of citronella oil as well as the PMRA's normal procedure for assessing applicable safety/uncertainty factors.

The PMRA will maintain the default application of the 100-fold safety/uncertainty factor for intraspecies and interspecies uncertainty. The PMRA considers the modification of this default safety/uncertainty factor when strong scientific data permit this to occur. The PMRA was unable to refine this factor because the data necessary to do so was not available for citronella oil. Additionally, to the best knowledge of the PMRA, the proposed default uncertainty factor refinement proposed by Dorne and Renwick (2005) and Dorne et al. (2005) has not been

accepted or utilized by other regulatory authorities. The PMRA is uncertain how such a refinement would be applied to a mixture containing many components.

The Panel further suggested that the additional 30-fold safety/uncertainty factor applied in the PMRA's original assessment was questionable. This additional factor was determined by and consistent with the PMRA's normal practice for assessing total applied safety/uncertainty factors. A copy of the PMRA's safety/uncertainty factor determination process was provided to the Panel for reference. However, application of the Panel's recommended new evaluation procedure (Monroe and Mattia 2004, Smith et al. 2005) altered the total safety/uncertainty factor applied to individual congeneric groups with the result that the maximum additional safety/uncertainty factor applied was 10-fold. The total applied safety/uncertainty factor applied for each congeneric group is identified in Appendix I.

Exposure Assessment and Dermal Absorption

Question 5
What does the Panel consider to be an appropriate dermal absorption value for citronella and related active ingredients? In answering this question, the Panel is asked to consider the compositional complexity and the physicochemical properties of these active ingredients.

Question 6
If a value of less than 100% is appropriate for dermal absorption, how would the Panel recommend accounting for the volatilised and potentially inhaled component as well as for the amount potentially ingested through hand-to-mouth contact?

Question 7
Can the Panel recommend other ways to refine the exposure assessment or suggest an alternative approach?

Summary of Panel Response and Recommendations

"These data suggest that the consideration of a dermal absorption fraction value of 1 may significantly overestimate the true absorption. Attempts should therefore be made to obtain dermal absorption data on major citronella oil constituents."

"To obtain a better estimate of volatilization, it is recommended that an experimental assessment be made."

"With regard to ingestion through hand-to-mouth contact, it can be disregarded because of the nasty taste of the citronella oil."

PMRA Response
As dermal absorption is chemical dependent, the PMRA, like other regulatory agencies, does not use surrogate values derived for different chemicals. Instead, the PMRA uses a weight-of-evidence approach considering all the data available, including the physical and chemical properties of the chemical and the specifics of the exposure scenario. Very limited chemical-

specific dermal absorption data are available for citronella. As noted in PACR2004-36, the physical-chemical characteristics of citronella oil include a high *n*-octanol–water partition coefficient and slight solubility in water. As well, one published study on citral suggests rapid absorption. These limited data suggest citronella would be well absorbed via the dermal route. However, the PMRA does agree with the Panel that few, if any, chemicals are 100% absorbed through the skin and that the assumption of 100% absorption could very likely be refined using additional data on citronella oil constituents. The Panel did not suggest using a specific, reduced default value, but, on reconsideration of all the data, the PMRA acknowledges that a reduced default value such as 50% may be more appropriate for risk assessment purposes.

The PMRA also agrees with the Panel that rat skin generally has greater permeability than human skin. However, the data available to quantify variability in dermal absorption, both within and between species, are limited. Confounding variables include species variability (e.g. Reifenrath 1984), variability between anatomic sites (e.g. Moody and Ritter 1989), the impact of different vehicles (Dick et al. 1977), the non-linear relationship between dermal dose and absorption, and the generally complex relationship between dose and serum/urinary levels. Consistent with the position of other pesticide regulatory jurisdictions, the PMRA does not currently consider the methodology for deriving quantitative adjustment factors on a generic basis to be sufficiently rigorous for regulatory use. For example, the European Commission concluded in 2002 that a generally applicable correction factor for extrapolation from laboratory animals to humans cannot be derived because the extent of overestimation appears to be dose, substance and animal specific (European Commission 2002). Appropriate chemical-specific rat and human data are not available to conduct this type of analysis on a chemical-specific basis for the constituents of citronella oil.

The PMRA agrees with the Panel that the constituents of citronella oil are volatile and this will also impact the degree of dermal absorption. However, as 100% dermal absorption was assumed, the PMRA did not assume any exposure through the inhalation route or through incidental hand-to-mouth transfer. If a refined value were available for dermal absorption, these exposure routes would require further consideration. A reduced default of 50% may still be considered to embrace enough conservatism to cover these additional exposure routes.

Risk Assessment

Question 8
Does the Panel concur with the risk assessment approach?

Question 9
Are there additional data and/or evidence that could help to address uncertainties in the risk assessment?

Question 10
If new information should be generated, what specifically would be most useful? In answering this question the Panel is asked to consider relevant routes of exposure and to identify the test materials that should be utilized, given the range of products encompassed by these natural oils.

Summary of Panel Response and Recommendations
The answers to questions 8, 9 and 10 are embedded in answers to previous questions.

PMRA Response
The PMRA' response is noted in its response to previous Panel input.

List of Abbreviations

µg	microgram
bw	body weight
CAS	Chemical Abstracts Service
CG	congeneric group
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavour and Extract Manufacturers Association
g	gram
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kg	kilogram
LOAEL	lowest observed adverse effect level
mg	milligram
MOE	margin of exposure
NA	not assigned
ND	not detected
NFC	natural flavour complex
NHP	natural health product
NHPD	Natural Health Products Directorate
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RIFM	Research Institute for Fragrance Materials
WHO	World Health Organization

Appendix I Application of the Procedure of Monroe and Mattia (2004), and Smith et al. (2005) to the Safety Assessment of Citronella Oil

A Overview

As recommended by the Panel, the protocol described by Monroe and Mattia (2004), and Smith et al. (2005) was utilized to conduct a hazard assessment of citronella oil. The procedure is based on the organization of constituents by congeneric group because members of each congeneric group have common structural features and, as a result, are expected to have similar pharmacokinetic and metabolic profiles and exhibit similar toxicologic potential. Any safety data available for any individual member of a congeneric group can be applied to the congeneric group as a whole based on expected similarities of metabolism and toxicological potential. Following a safety assessment of each congeneric group, an evaluation of all the congeneric groups together is completed to account for any chemical or biological interactions between congeneric groups. A final comparison is made between the evident or predicted toxicity by this protocol and any available toxicity data for the whole oil. Overall, this safety evaluation procedure permits the conduct of a risk assessment for either a natural flavouring complex (NFC) or individual constituents where little data are available, as is the case for citronella oil.

Table 1 provides an approximate composition of citronella oil and assigns a congeneric group and toxicity class to each component of citronella oil. Congeneric group and toxicity class assignments were based on published literature and in consultation with the Flavor and Extracts Manufacturer Association (FEMA).

Table 2 provides a summary of available toxicity data judged to be applicable to assessment of toxicity for each congeneric group. It should be noted that not all chemicals noted in this table are constituents of citronella oil. Where such chemicals have been included, they are members of the congeneric group identified and, by definition, should reflect the toxicity of the group.

Table 3 provides calculated exposure values by congeneric group.

Tables 4 and 5 provides calculated margin of exposure (MOE) values resulting from a qualitative risk assessment.

B Step-by-Step Evaluation Process

The evaluation process as applied to citronella oil is outlined below based on the flow chart presented in Monroe and Mattia (2004). The path taken through the procedure is indicated by bolded text. For each step taken, relevant discussion is provided.

Step 1: Determine the structural class for the flavouring agent or congeneric group in the flavouring agent or NFC (see notes 1, 3).

Discussion
See Appendix I, Table 1 for citronella oil constituent composition sorted by congeneric group, with toxicity class assignments noted.

Step 2: Can the flavouring agent or congeneric group of flavouring agents be predicted to be metabolized by well recognized detoxification pathways to yield innocuous products?

To Step 3A if yes.

To Step 3B if no.

Discussion

The majority of the constituents of citronella oil are predicted to be metabolized by well recognized detoxification pathways, yielding innocuous products when exposure is by the oral route and at normal food level exposure levels (very low). However, for citronella oil incorporated in insect repellent products, the primary exposure pathway is dermal and exposure, relative to food uses, is very high. Little data are available to characterize dermal absorption, dermal metabolic products and toxicokinetics following dermal exposure. Therefore, even though the components are expected to be metabolized by well recognized detoxification pathways, pathways A and B were followed due to the uncertainty present.

Step 3A: Do the conditions of use of the flavouring agent or congeneric group result in an intake greater than the threshold of concern for the structural class?

To Step 4A if yes.

3A1 If no, the substance or congeneric group would not be expected to be a safety concern. Following evaluation of all congeneric groups in the flavouring agent or NFC, proceed to Step 6A (see Note 2).

Discussion

The threshold of concern values indicated in Smith et al. (2005) and Monroe and Mattia (2004) were adjusted to reflect the default body weight used by the PMRA. The threshold values were originally calculated based on a default adult body weight of 60 kg. The PMRA assumes a default adult body weight of 70 kg. Appendix I, Table 3 indicates, for each congeneric group, if the threshold of concern defined by the World Health Organization (WHO) for assessment of food safety has been exceeded. See Appendix I Part D for limitations related to this assessment.

Step 3B: Do the conditions of use of the flavouring agent or congeneric group result in an intake greater than the threshold of concern for the structural class?

To Step 4B if no.

3B1 If yes, adequate data must be available on the substance to perform a safety evaluation based on intake (see Note 3).

Evaluation process complete. Completion of a risk assessment, based on available data would follow the same process noted in the discussion for Step 5A.

Discussion:
The threshold of concern values indicated in Smith et al. (2005) and Monroe and Mattia (2004) were adjusted to reflect the default body weight used by the PMRA. The threshold values were originally calculated based on a default adult body weight of 60 kg. The PMRA assumes a default adult body weight of 70 kg. Appendix I, Table 3 indicates, for each congeneric group, if the threshold of concern defined by WHO for assessment of food safety has been exceeded. **See Appendix I Part D for limitations related to this assessment.**

Step 4A: Is the substance, or are its metabolites, or all members of the congeneric group, endogenous?

To Step 3A1 if yes.

To Step 5A if no.

Discussion:
Not all constituents or their metabolites of the identified congeneric groups are endogenous.

Step 4B: **[Step not necessary]** Does a no observed effect level (NOEL) that provides an adequate margin of safety under conditions of intended use exist for the substance or does a NOEL that is high enough to accommodate any perceived difference in toxicity among members of the congeneric group exist for members of the congeneric group?

4B1 If yes, the substance or congeneric group would not be expected to be of safety concern. Following evaluation of all congeneric groups in the flavouring agent or NFC, proceed to Step 6B.

To Step 5B if no.

Step 5A: Does a NOEL that provides an adequate MOE under conditions of intended use exist for the substance or does a NOEL that is high enough to accommodate any perceived difference in toxicity among members of the congeneric group exist for members of the congeneric group?

If yes, the substance or congeneric group would not be expected to be of safety concern. Following evaluation of all congeneric groups in the flavouring agent or NFC, proceed to Step 6A (see Note 2).

If no: additional data required.

Evaluation process complete.

Discussion
See Appendix I, Table 2 for the citronella oil toxicology table separated by congeneric group. See tables 4 and 5 for MOE calculations for each congeneric group for adults following one application of products containing either 15% or

10% citronella oil and a 50% dermal absorption value. These tables provide exposure values, applicable NOAEL values, applicable uncertainty/safety factors, and calculated MOE values for each congeneric group. Multiple congeneric groups did not achieve target MOE values indicating that continued registration of citronella oil cannot be supported. Child MOE calculation tables were not prepared because child exposure, on a mg/kg bw/day basis, is higher than adult exposure. Since required MOE values were not achieved for the adult, calculated values for children would not be expected to achieve required MOE values. **See Appendix I Part D for limitations related to this assessment.**

Step 5B: **[Step not necessary]** Do the conditions of use result in an intake greater than 1.5 µg/day?

If no, the substance or congeneric group would not be expected to be of safety concern. Following evaluation of all congeneric groups in the flavouring agent or NFC, proceed to Step 6B (see Note 2).

If yes, additional data are required.

Step 6A/B: **[Step not necessary]** Are all of the congeneric groups in the flavouring agent or NFC determined to be of no safety concern?

If yes, the flavouring agent or NFC would not be expected to be a safety concern.

If no, additional data are required.

Notes for the procedure:

1: If members of the congeneric group have different structural classes, assign the highest structural class to the congeneric group. If the flavouring agent or natural flavouring complex contains more than one congeneric group, assign a decision tree classification to each of the congeneric groups that make up the flavouring agent or natural flavouring complex.

2: Step 6A and 6B are not applicable to individual flavouring agents with assay values of >95%.

3: This step was revised by the Committee at its sixty-first meeting when it noted that more extensive data rare required to perform a safety evaluation of flavouring agents with intakes above the threshold of concern for their structural class. Such data would include metabolism and toxicity data on the substance. Refined estimates of exposure may be needed. Data on structurally related substances may be used to support the evaluation.

C Qualitative Risk Assessment

The information presented in Tables 3, 4 and 5 represent a *qualitative* risk assessment only. The qualitative risk assessment was necessary to complete the evaluation protocol of Smith et al. (2005) and Monroe and Mattia (2004) in Step 5A as well as to examine the feasibility of conducting additional studies. Adequate data to conduct a risk assessment were not available for all congeneric groups or exposure durations. Recognizing that the default assumption of 100% dermal absorption used in the risk assessment outlined in PACR2004-36, *Re-evaluation of Citronella Oil and Related Active Compounds for Use as Personal Insect Repellents*, was very conservative, a dermal absorption value of 50% was used in the risk assessment.

It must be recognized that no data are available to support the use of 50% dermal absorption; therefore, the risk assessment represents a 'what if' scenario. Each constituent of citronella will have an individual dermal absorption value, which may be affected by the presence of the other constituents of citronella oil and by its volatility. A consequence of these factors is that the 'citronella oil' seen systemically could be different orally and dermally, leading to a difference in observed NOAELs and toxicities between the oral and dermal routes of exposure.

D Data Required to Complete a Quantitative Risk Assessment

Application of the outcome of the evaluation procedure of Smith et al. (2005) and Monroe and Mattia (2004) demonstrates that additional data is necessary to complete a quantitative risk assessment for citronella oil. Examination of Table 2 shows there is a lack of data for citronella oil. In addition, with respect to the completion of a hazard and risk assessment by the procedure of Smith et al. (2005) and Monroe and Mattia (2004), several congeneric groups lack critical studies necessary to fully describe the potential toxicity of those groups and, consequently, citronella oil. There is also a lack of studies conducted by the dermal route of exposure. The primary toxicological concerns identified from the available data as a whole are reproductive and developmental endpoints. These are the most sensitive endpoints and are likely to drive the determination of NOAEL values in new studies of citronella oil toxicity.

As the toxicities of most concern are reproductive and developmental, data submitted to address the uncertainties in the current risk assessment must address these endpoints. Separate or combined reproduction and developmental studies may be conducted, by either the oral or the dermal route. Study options are presented below. The preferred option is to conduct a combined study via the dermal route of exposure because this will directly assess the endpoints of concern by the most relevant route and does not need to include a complex determination of dermal absorption.

Option 1: Two-generation rat reproduction study by oral route of exposure with whole citronella oil; and
- rat developmental toxicity by oral route of exposure with whole oil; and
- dermal absorption study with whole citronella oil.

Option 2: One-generation reproduction study with developmental toxicity endpoints by the dermal route of exposure with whole citronella oil. A study of

dermal dosing tolerance may be necessary to ensure it is possible to conduct the main study without having to remove animals due to adverse skin irritation.

Prior to conducting any study, the registrant is required to discuss the study protocols with the PMRA. The conduct of these studies will require modification of traditional study design protocols.

The registrants are strongly encouraged to form a task force to jointly finance data development.

Table 1 Approximate Chemical Composition of Citronella Oil (Java) and Congeneric Group Assignments

Compound	%	Total % CG	Chemical Group Name	CG[1]	Toxicity class[1]	FEMA number CAS number
decanal	0.1	0.1	Straight-chain primary aliphatic alcohols/aldehydes/acids, acetals and esters	1	1	2362 112-31-2
cis-3-hexenol*	0.01	28.3	Alpha, beta- unsaturated (alkene or alkyne) straight-chain and branched-chain aliphatic primary alcohols/aldehydes/acids, acetals and esters	3	1	2563 928-96-1
neryl acetate	0.04		Alpha, beta- unsaturated (alkene or alkyne) straight-chain and branched-chain aliphatic primary alcohols/aldehydes/acids, acetals and esters	3	1	2773 141-12-8
geranyl acetate	5.07		Alpha, beta- unsaturated (alkene or alkyne) straight-chain and branched-chain aliphatic primary alcohols/aldehydes/acids, acetals and esters	3	1	2509 105-87-3
geraniol	23.18		Alpha, beta- unsaturated (alkene or alkyne) straight-chain and branched-chain aliphatic primary alcohols/aldehydes/acids, acetals and esters	3	1	2307 106-24-1
trans-alpha-farnesol*	0.08	48.26	Non-conjugated and accumulated unsaturated straight-chain and branched chain aliphatic primary alcohols/aldehydes/acids, acetals and esters	4	1	NA
melonal	0.09		Non-conjugated and accumulated unsaturated straight-chain and branched chain aliphatic primary alcohols/aldehydes/acids, acetals and esters	4	1	2389 106-72-9
cis-alpha-farnesol	0.1		Non-conjugated and accumulated unsaturated straight-chain and branched chain aliphatic primary alcohols/aldehydes/acids, acetals and esters	4	1	NA

Compound	%	Total % CG	Chemical Group Name	CG[1]	Toxicity class[1]	FEMA number CAS number[1]
citronellic acid	0.13		Non-conjugated and accumulated unsaturated straight-chain and branched chain aliphatic primary alcohols/aldehydes/acids, acetals and esters	4	1	3142 502-47-6
citronellyl acetate	1.88		Non-conjugated and accumulated unsaturated straight-chain and branched chain aliphatic primary alcohols/aldehydes/acids, acetals and esters	4	1	2311 150-84-5
citronellol	11.19		Non-conjugated and accumulated unsaturated straight-chain and branched chain aliphatic primary alcohols/aldehydes/acids, acetals and esters	4	1	2309 106-22-9
citronellal	34.79		Non-conjugated and accumulated unsaturated straight-chain and branched chain aliphatic primary alcohols/aldehydes/acids, acetals and esters	4	1	2307 106-23-0
6-methyl-5-hepten-2-one	0.01	0.01	Saturated and unsaturated aliphatic secondary alcohols/ketones/ketals/esters with esters containing secondary alcohols	5	2	2707 110-93-0
terpinen-4-ol	0.04	5.48	Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters containing tertiary alcohols	6	1	2248 562-74-3
alpha-terpineol	0.05		Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters containing tertiary alcohols	6	1	3045 98-55-5
alpha-terpinyl acetate (terpinyl acetate)	0.16		Aliphatic,alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters containing tertiary alcohols	6	1	3047 (mixed isomer) NA 80-26-2 (alpha isomer)
10-epi-gamma-eudesmol*	0.17		Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters containing tertiary alcohols	6	1	NA NA
trans-muurolol	0.53		Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters containing tertiary alcohols	6	1	NA 19912-62-0
T-amorphol/bulnesol*	0.65		Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters containing tertiary alcohols	NA/6	1	NA 22451-43-6
linalool	0.72		Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters containing tertiary alcohols	6	1	2635 78-70-6
elemol	3.16		Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters containing tertiary alcohols	6	1	NA 639-99-6

Compound	%	Total % CG	Chemical Group Name	CG[1]	Toxicity class[1]	FEMA number CAS number
borneol	0.05	0.27	Secondary alicyclic saturated and unsaturated alcohols/ketones/ketals/esters	8	1	2157 507-70-0
iso(iso)pulegol*	0.22		Secondary alicyclic saturated and unsaturated alcohols/ketones/ketals/esters	8	I	2962 89-72-9
beta-phellandrene / 1,8-cineole	0.07	0.07	Aliphatic and alicyclic ethers	31/16	39083	NA / 2465 555-10-2 / 470-82-6
methyl eugenol	0.09 (≥3)	2.54	Allylhydroxybenzenes	18	3	2475 93-15-2
eugenol	2.45		Allylhydroxybenzenes	18	1	2467 97-53-0
delta-elemene*	0.01	12.58	Aliphatic and aromatic hydrocarbons	31	1	NA 20307-84-0
alpha-terpinene	0.01		Aliphatic and aromatic hydrocarbons	31	1	3558 99-86-5
delta-3-carene	0.01		Aliphatic and aromatic hydrocarbons	31	1	3821 13466-78-9
beta-pinene	0.01		Aliphatic and aromatic hydrocarbons	31	1	2903 127-91-3
tricyclene	0.01		Aliphatic and aromatic hydrocarbons	31	1	NA 508-32-7
camphene	0.04		Aliphatic and aromatic hydrocarbons	31	1	2229 79-92-5
alpha-pinene	0.05		Aliphatic and aromatic hydrocarbons	31	1	2903 80-56-8
terpinolene	0.06		Aliphatic and aromatic hydrocarbons	31	1	3046 586-62-9
beta-phellandrene/ 1,8-cineole	0.07		Aliphatic and aromatic hydrocarbons	31/16	39083	NA/2465 555-10-2 / 470-82-6
sabinene	0.07		Aliphatic and aromatic hydrocarbons	31	1	NA 3387-41-5
alpha-copaene*	0.08		Aliphatic and aromatic hydrocarbons	31	1	NA 3856-25-5
myrcene	0.09		Aliphatic and aromatic hydrocarbons	31	1	2762 123-35-3
beta-bourbonene	0.1		Aliphatic and aromatic hydrocarbons	31	1	NA 2508-59-3
alpha-humulene	0.13		Aliphatic and aromatic hydrocarbons	31	1	NA 6753-98-6
trans-beta-ocimene	0.19		Aliphatic and aromatic hydrocarbons	31	1	3539 13877-91-3

Compound	%	Total % CG	Chemical Group Name	CG[1]	Toxicity class[1]	FEMA number CAS number
beta-caryophyllene	0.22		Aliphatic and aromatic hydrocarbons	31	1	2252 87-44-5
cis-beta-ocimene	0.37		Aliphatic and aromatic hydrocarbons	31	1	NA 3338-55-4
alpha-muurolene*	0.46		Aliphatic and aromatic hydrocarbons	31	1	NA 10208-80-7
gamma-muurolene*	0.67		Aliphatic and aromatic hydrocarbons	31	1	NA 30021-74-0
delta-cadinene	1.17		Aliphatic and aromatic hydrocarbons	31	1	1346 (isomer mixture) 483-76-1
gamma-cadinene	1.74		Aliphatic and aromatic hydrocarbons	31	1	1346 (isomer mixture) 39029-41-9
beta-elemene	1.96		Aliphatic and aromatic hydrocarbons	31	1	NA 33880-83-0
beta-cubebene*	2.25		Aliphatic and aromatic hydrocarbons	31	1	NA 13744-15-5
limonene	2.81		Aliphatic and aromatic hydrocarbons	31	1	2633 5989-27-5
Total % of oil	97.6					

* Not previously reported in citronella oil
The beta-phellandrene/1,8-cineole and T-amorphol/bulnesol peaks did not consistently separate.
NA = not assigned
Notes:
1. These values were assigned based on published information for individual constituents of citronella oil and on information supplied by FEMA.

Table 2 Available Toxicity Data and Endpoint Selection by Congeneric Group

Toxicology Table for Congeneric Group 1 (~0.1% of citronella)			
Study/Species / # of Animals per Group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
SUBCHRONIC TOXICITY STUDIES			
Not available			
CHRONIC TOXICITY / ONCOGENICITY STUDIES			
Not available			
REPRODUCTIVE AND DEVELOPMENTAL TOXICITY STUDIES			
Not available			
GENOTOXICITY STUDIES			
Not available			

Endpoint selection and indicated safety/uncertainty factors for congeneric group 1
Not possible due to lack of data

Toxicology Table for Congeneric Group 3 (~28% of citronella)			
Study/Species / # of Animals per Group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
SUBCHRONIC TOXICITY STUDIES			
CITRAL (published studies)			
2-week oral (gavage) toxicity—F344 rat, 5/sex/dose	(purity unknown); 0, 570, 1140, 2280 mg/kg	NOAEL = 1140	No effects on mortality, body weight or histopathology; minimal hyperplasia of squamous epithelium of glandular stomach in 2 males at the highest dose.
14-week dietary toxicity— F344/N rat, 10/sex/dose	0, 3900, 7800, 15 600, 31 000 ppm (0, 345/335, 820/675, 1785/1330 mg/kg/day, ♂/♀)	NOAEL = 335 (♂)	≥ 335 mg/kg: ↓ mean body weight (5, 13, 27, ND % for males; 5, 4, 12, ND % for females in the low, low mid, high mid and high dose groups, respectively. High dose groups died prematurely) ≥ 675 mg/kg: ↓ food intake during first week of the study ≥ 1330 mg/kg: All rats killed moribund in second week of the study, and showed signs of listlessness, hunched posture, absent or slow paw reflex, dull eyes; fore stomach epithelial hyperplasia, hyperkeratosis, bone marrow atrophy and haemorrhage, nephrotoxicity

Toxicology Table for Congeneric Group 3 (~28% of citronella)			
Study/Species / # of Animals per Group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
14-day oral (gavage) toxicity— mouse, 5/sex/dose	0, 534, 1068, 2137 mg/kg	NOAEL = 534	≥1068 mg/kg: ↑ mortality in ♂; ↑ liver weight, vacuolization of hepatocytes in ♀ at 1068 mg/kg and in ♂ at 2137 mg/kg. 2137 mg/kg: ↑ mortality and necrosis of fore stomach in both sexes
14-week dietary toxicity— B6C3F1 mice, 10/sex/dose	0, 3900, 7800, 15600, 31000 ppm (= 0, 745/790, 1840/1820, 3915/3870, 8110/7550 mg/kg/day, ♂/♀)	NOAEL not set LOAEL = 745	≥ 745 mg/kg: ↓ mean bw (15/12% in males/females); ↑ food consumption by the end of the study ≥ 1820 mg/kg: ↑ food intake during first week (♀); a few males thin ≥ 3870 mg/kg: thinness and lethargy; ↑ incidence of ovarian atrophy; mild forestomach hyperkeratosis and epithelial hyperplasia (♀) 8110 mg/kg: 4 males killed moribund by second week
GERANIOL			
16-week feed— rat	10 000 ppm	NOAEL = 10 000 ppm	No effects
16-week feed— rat	1000 ppm	NOAEL = 1000 ppm	No effects
27- to 28-week feed— Osborne-Mendel rat, 10/sex/dose	1000 ppm	NOAEL = 1000 ppm	No effects
GERANYL ACETATE			
12-week feeding—rat, 15/sex/dose	48.4 mg/kg bw/day	LOAEL = 48.4	Slight retardation of growth in females (questionable)
17 week feeding— Osborne-Mendel rat, 10/sex/dose	0, 0.1, 0.25, 1.0%	NOAEL = 500	No effects
CHRONIC TOXICITY / ONCOGENICITY STUDIES			
CITRAL (published studies)			
2-year bioassay— F344/N rat, 50/sex/dose	0, 1000, 2000, 4000 ppm (0, 50, 100, 210 mg/kg/day)	NOAEL = 100	≥ 50 mg/kg: ↑ survival (♂) 210 mg/kg: ↓ mean body weight from ≥ 49 weeks (♂) or ≥ 25 weeks (♀) **No evidence of carcinogenicity**

Toxicology Table for Congeneric Group 3 (~28% of citronella)			
Study/Species / # of Animals per Group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
2-year bioassay—B63CF$_1$ mice, 50/sex/dose	0, 500, 1000, 2000 ppm (0, 60, 120, 260 mg/kg/day)	NOAEL not set LOAEL = 60	≥ 60 mg/kg: ↓ mean body weight from 30 weeks (♀); a positive trend for incidence of malignant lymphoma (spleen, mesenteric lymph node, thymus) in females (3/49, 5/50, 9/50 and 12/50 at 0, 0, 60, 120, 260 mg/kg/day, respectively) ≥ 120 mg/kg: ↓ mean body weight throughout the study (♂) 260 mg/kg: ↑ incidence of malignant lymphoma (♀) (24% versus 6% in controls), statistically significant in high dose, but within historical control range for the National Toxicology Program. **No evidence of carcinogenicity in male mice; equivocal evidence of carcinogenicity in female mice.**
GERANYL ACETATE / CITRONELLYL ACETATE			
103 weeks gavage—F344/N rats, 50/sex/dose	Geranyl acetate/ citronellyl acetate (71%/29%) 1000, 2000 mg/kg bw in corn oil	NOAEL = 1000	Decreased survival in high dose (male: 34/50, 29/50, 18/50). Decreased body weight in high dose animals. Kidney tubular cell adenomas (uncommon): 2/50 (4%) in low dose males. Historical control: 1/250 (0.4%). Squamous cell papillomas marginally increased in low dose males (0/50, 4/50 [8%], 1/50 [2%]. Squamous cell carcinoma 1/50 low dose male. Combined skin tumours greater than controls ($p < 0.05$). Historical control combined tumours: 9/250 (3.6%). Incidence of all epidermal tumours combined not different than controls. Reduced survival in high dose animals may have reduced sensitivity of the assay. **Not carcinogenic**

Toxicology Table for Congeneric Group 3 (~28% of citronella)			
Study/Species / # of Animals per Group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
REPRODUCTIVE AND DEVELOPMENTAL TOXICITY STUDIES			
CITRAL (published studies)			
One-generation, 1-litter dermal reproductive toxicity— virgin Wistar rat, 19-20 ♀/dose	0, 460 mg/kg for 60 or 100 days premating (i.e. animals not treated during pregnancy and the 21-day nursing period); dams and pups killed 21 days postpartum	NOAEL for maternal toxicity > 460 NOAEL for reproductive toxicity not set (LOAEL = 460) NOAEL for offspring toxicity not set (LOAEL = 460)	Maternal toxicity: No apparent toxic effects Reproductive toxicity: 28% postimplantation loss (60 days) and 31.8% postimplantation loss (100 days) versus 7.4% postimplantation loss in the control group; ↓ number of implantation sites, ↓ litter size, ↓ number of primordial and primary follicles, degeneration of ovarian follicles and ↓ number corpora lutea in dams treated prior to mating only for 100 days Offspring toxicity: All offspring from dams treated topically for 100 days died in first week of birth (↓ offspring survival) **Evidence of (delayed) reproductive and embryofetal toxicity, and increased fetal/offspring sensitivity**
Oral (gavage) teratogenicity— Wistar rat, 19–20 ♀/group	0, 60, 125, 250, 500, 1000 mg/kg; gestation days 6–15	Maternal NOAEL not set Developmental NOAEL = 60	Maternal effects: ↓ food intake and weight gain at ≥ 60 mg/kg Reproductive effects:↓ implantation, live fetuses/dam at ≥ 125 mg/kg Developmental effects: ↓ live fetuses at 125 and 1000 mg/kg bw/day, ↑ spleen weight at 125 mg/kg bw/day. Delayed ossification at ≥ 125 mg/kg (incidence not dose-related) **No evidence of teratogenicity or fetal sensitivity in rats**
Oral (gavage) reproduction screening assay (OECD 421)— Cij:CD(SD) rat, 12/sex/group	**Citral** (purity 98.2%: 54.99% **geranial**; 43.6% **neral**) 0, 40, 200, 1000 mg/kg bw/day in corn oil Males: 46 days Females: 39–50 days (14 day prior to mating to day 3 lactation)	Systemic NOAEL = 200 Reproductive NOAEL = 1000 Offspring NOAEL = 200	1000 mg/kg bw/day: ↓ body-weight gain and food consumption (at day 5 both sexes; day 4 lactation). Dilation of renal pelvis, testis/epididymis atrophy, discolouration of liver, thickening of forestomach mucose (females), squamous hyperplasia, ulcer and cellular infiltration of neutrophils and granulation in the lamina propria (females) Offspring: 1000 mg/kg: significant decreases in body weight in pups during lactation.

Toxicology Table for Congeneric Group 3 (~28% of citronella)			
Study/Species / # of Animals per Group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
GENOTOXICITY STUDIES			
CITRAL			
Ames Salmonella TA97a, TA98, TA100, TA102	100–700 µg/plate ± S9		negative
Ames Salmonella Test; TA98, TA100, TA1535, 1537	1–220 µg/plate ± S9		negative
Ames Salmonella test; TA98, TA100, TA1535, TA1537, TA1538	culture ± S9		negative
Sister chromatid exchange—Chinese hamster ovary cells	culture ± S9		positive
Chromosomal aberration—Chinese hamster ovary cells	culture ± S9		negative
In vivo bone marrow micronucleus—B6C3F1 mice	0, 250 to 750 mg/kg/day for 3 days (intraperitoneal)		negative
GERANIOL			
Ames Salmonella Test; TA 92, 94, 98, 100, 1535, 1537	0.5 mg/mL		± S9: negative
Chromosomal abberation (Chinese hamster fibroblasts)	0.125 mg/mL		- S9: positive

Endpoint selection and indicated safety/uncertainty factors for congeneric group 3
Endpoint selection for acute-duration dermal exposure NOAEL = 60 mg/kg bw/day based on a rat developmental study in which ↓ implantations and live fetuses at 125 mg/kg bw/day were observed Endpoint selection for intermediate-duration dermal exposure NOAEL = 60 mg/kg bw/day based on a rat developmental study in which ↓ implantations and live fetuses at 125 mg/kg bw/day were observed Safety/uncertainty factors 10 intraspecies factor 10 interspecies factor

Toxicology Table for Congeneric Group 4 (~48% of citronella)			
Study/Species / # of Animals per Group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
SUBCHRONIC TOXICITY STUDIES			
CITRONELLOL / LINALOOL 50/50			
12-week dietary—rat, 10/sex/dose	50 mg/kg bw/day	NOAEL = 50	Significant depression of body weight and food intake due to palatability issues. No significant changes in appearance, urinalysis, blood hemoglobin, liver and kidney weights or gross pathology
90-day feed—rat, 10/sex/dose	100 mg/kg bw/day	NOAEL = 100	Food intake and weight gain were significantly depressed in males; however, the authors attributed this to poor palatability
CHRONIC TOXICITY / ONCOGENICITY STUDIES:			
Not available			
REPRODUCTIVE AND DEVELOPMENTAL TOXICITY STUDIES			
Not available			
GENOTOXICITY STUDIES			
CITRONELLAL			
Ames Salmonella test (his-)	0.05–500 µg/plate ± S9	negative	
Ames Salmonella Test; TA97a, TA98, TA100, TA102	5–200 µg/plate ± S9	negative	
Sister chromatid exchange—Chinese hamster ovary cells	3.3–100 µmol/l (0.51–15.4 µg/mL) - S9	negative	
Chromosomal aberration—Chinese hamster B241 cells	50 nmol/l (0.008 µg/mL) + S9	weakly positive	

Endpoint selection and indicated safety/uncertainty factors for congeneric group 4
Endpoint selection for acute-duration dermal exposure No applicable data Endpoint selection for intermediate-duration dermal exposure NOAEL = 100 mg/kg bw/day in a 90-day oral rat study without treatment related effects. Safety/uncertainty factors 10 intraspecies factor 10 interspecies factor 10 database uncertainties

Toxicology Table for Congeneric Group 5 (~0.01% of citronella)			
Study/Species / # of Animals per Group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
SUBCHRONIC TOXICITY STUDIES			
Not available			
CHRONIC TOXICITY / ONCOGENICITY STUDIES:			
Not available			
REPRODUCTIVE AND DEVELOPMENTAL TOXICITY STUDIES			
Not available			
GENOTOXICITY STUDIES			
Not available			

Endpoint selection and indicated safety/uncertainty factors for congeneric group 5
Not possible due to lack of data

Toxicology Table for Congeneric Group 6 (~5% of citronella)			
Study/Species / # of animals per group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
SUBCHRONIC TOXICITY STUDIES:			
CITRONELLOL / LINALOOL 50/50			
12-week dietary—rat 10/sex/dose	50 mg/kg bw/day	NOAEL = 50	Significant depression of body weight and food intake due to palatability issues. No significant changes in appearance, urinalysis, blood hemoglobin, liver and kidney weights or gross pathology
90-day feed—rat 10/sex/dose	100 mg/kg bw/day	NOAEL = 100	food intake and weight gain were significantly depressed in males however, the authors attributed this to poor palatability

Toxicology Table for Congeneric Group 6 (~5% of citronella)			
Study/Species / # of animals per group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
LINALYL ESTERS			
17- to 18-week feed— Osborne-Mendel rat 10/sex/dose	1: Linalyl cinnamate 2: Linalyl isobutyrate 50, 125, 500 mg/kg bw/day	Linalyl cinnamate NOAEL = 500 Linalyl isobutyrate NOAEL = 500	No effects
LINALOOL			
Dermal—rat 29 days (Wistar) (range finding for 90 day) 2/sex/dose Dermal Rat, 91 days (Sprague-Dawley) 20/sex/dose	250–4000 mg/kg bw/day	Dermal and systemic LOAEL = 250	29 day study: ≥250 mg/kg bw/day: 1 male died on day 7. Dermal irritation and the following toxic signs were observed at all dose levels and were dose related: lethargy, ataxia, piloerection and discomfort. Moderate to severe erythema and slight to moderate edema. Bleeding, scabbing and moderate eschar were noted in one or more animals at each dose level. Alakline phosphatase values were elevated in a dose related manner. Slight to moderate epithelial hyperplasia of the treated skin was observed at histopathology. 4000 mg/kg bw/day: 1 female died day 26; decreased body-weight gain in males and females and elevated glucose and cholesterol mean values were observed at the highest dose only 90 day study: ≥250 mg/kg bw/day: Slight erythema that cleared after 3 weeks; depressed activity ≥1000 mg/kg bw/day: Body weight depressed in females; slight erythema which cleared after 6 weeks 4000 mg/kg bw/day: 11 deaths (9 female/2 male); ↑ liver weight; ↑ kidney weight in females; slight to moderate epithelial hyperplasia; slight erythema, lethargy in females
CHRONIC TOXICITY / ONCOGENICITY STUDIES			
Not available			
REPRODUCTIVE AND DEVELOPMENTAL TOXICITY STUDIES			
Not available			
GENOTOXICITY STUDIES			
LINALOOL			

Toxicology Table for Congeneric Group 6 (~5% of citronella)			
Study/Species / # of animals per group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
Bacterial reverse mutation ± S9 (TA98, TA100, TA1535, TA1537, TA1538)	**linalool** ≥5000 µg/plate	Negative	
E. coli WP2uvrA (± S9 not stated)	**linalool** 0.125–1.0 mg/plate	Negative	
Bacterial DNA repair B. subtilis H17 and M45 (± S9 not stated)	**linalool** max concentration 10 µL/disk	Negative	
Unscheduled DNA synthesis, rat hepatocytes	**linalool** 0.50 µg	Negative	
Mammalian gene mutation (mouse lymphoma L5178Y TK+) ± S9	**linalool** 150, 200 µg/mL ± S9	Positive	
Chromosomal abberation (Chinese hamster fibroblasts) - S9	**linalool** 0.25 mg/mL	Negative	

Endpoint selection and indicated safety/uncertainty factors for congeneric group 6

Endpoint selection for acute-duration dermal exposure

Dermal and systemic LOAEL = 250 mg/kg bw/day established in a 29- and 90-day dermal study and based on dermal irritation/histopathology and decreased activity levels

Endpoint selection for intermediate-duration dermal exposure

Dermal and systemic LOAEL = 250 mg/kg bw/day established in a 29- and 90-day dermal study and based on dermal irritation/histopathology and decreased activity levels

Safety/uncertainty factors

10 intraspecies factor
10 interspecies factor
10 database uncertainties / use of LOAEL

Toxicology Table for Congeneric Group (~0.3% of citronella)			
Study/Species / # of Animals per Group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
SUBCHRONIC TOXICITY STUDIES			
Not available			
CHRONIC TOXICITY / ONCOGENICITY STUDIES			
Not available			
REPRODUCTIVE AND DEVELOPMENTAL TOXICITY STUDIES			
Not available			
GENOTOXICITY STUDIES			
Not available			

Endpoint selection and indicated safety/uncertainty factors for congeneric group 8
Not possible due to lack of data

Toxicology Table for Congeneric Group 16 (~0.07% of citronella)			
Study/Species / # of animals per group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
SUBCHRONIC TOXICITY STUDIES			
Not available			
CHRONIC TOXICITY / ONCOGENICITY STUDIES			
Not available			
REPRODUCTIVE AND DEVELOPMENTAL TOXICITY STUDIES			
Not available			
GENOTOXICITY STUDIES			
Not available			

Endpoint selection and indicated safety/uncertainty factors for congeneric group 16
Not possible due to lack of data

Toxicology Table for Congeneric Group 18 (~2.5% of citronella)			
Study/Species / # of Animals per Group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
SUBCHRONIC TOXICITY STUDIES			
EUGENOL			
19-week feed—Osborne-Mendel rat, 10/sex/dose	**Eugenol** 1000, 10 000 ppm	1000 ppm	No macroscopic effects.
34-day gavage—Osborne-Mendel rat, 20 male	**Eugenol** Max dose 4000 mg/kg in corn oil	ND	Initial dose 1400 mg/kg increased gradually to 4000 mg/kg. 8 animals survived 34 days; 15 survived to receive 4000 mg/kg dose. Stomach: macroscopic findings—forestomach mucosa showed coalescent areas covered by thick flaky white material punctuated by minute ulcers; microscopic findings—moderately severe hyperkeratosis of the stratified squamous epithelium in the forestomach. Bone—slight osteoporosis.
13-week feeding—F344/N rat 10/sex/dose	**Eugenol** 0, 800, 1500, 3000, 6000, 12 500 ppm	NOAEL = 6000 ppm	12 500 ppm: male and female body weights 10% and 6% less than control values. No compound related histopathological findings.
13-week feeding—B6C3F1 mice, 10/sex/dose	**Eugenol** 0, 400, 800, 1500, 3000, 6000 ppm	NOAEL = 6000 ppm	No significant body weight, survival or histopathological effects noted.
CHRONIC TOXICITY / ONCOGENICITY STUDIES			
EUGENOL			
103-week dietary—F344/N rat, 50/sex/dose	**Eugenol** Males: 0, 3000, 6000 ppm (128, 261 mg/kg bw/day) Females: 0, 6000, 12 500 ppm (305, 1538 mg/kg bw/day)	NOAEL: 6000 ppm	High dose female body weights significantly reduced. No survival or food consumption differences. No treatment related tumours. Not carcinogenic.
103-week—B6C3F1 mice, 50/sex/dose	**Eugenol** 0, 3000, 6000 ppm (Male: 627, 1237 mg/kg bw/day Female: 731, 1407 mg/kg bw/day)	NOAEL (females): 3000 ppm NOAEL (males): 6000 ppm	High dose female body weights significantly reduced. No survival or food consumption differences. In male mice: significantly increased incidence of hepatocellular adenomas and carcionomas in low dose group only. In female mice: no single tumour type significantly increased, however, there was a significant dose related trend for the combined incidence of hepatocellular adenomas and carcinomas. Equivocal evidence of carcinogenicity.

Toxicology Table for Congeneric Group 18 (~2.5% of citronella)			
Study/Species / # of Animals per Group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
REPRODUCTIVE AND DEVELOPMENTAL TOXICITY STUDIES			
Not available			
GENOTOXICITY STUDIES			
EUGENOL			
Chromosomal recombination assay—*Saccharomyces cervisiae*, strain RS9	**Eugenol** 0.65–2.27 mM ± S9		positive
Ames Salmonella; TA97, TA98, TA100, TA102	**Eugenol** 0.25–9.00 mM ± S9		negative: TA97, TA100 weak positive: TA98, TA102 ± S-9 fraction
Ames Salmonella; TA100,TA1535, TA98, TA1537, TA1538	**Eugenol** (98.9% purity) 60–600 µg/plate ± S9		negative
Unscheduled DNA synthesis—rat primary hepatocytes	**Eugenol** 10^{-6}–10^{-3} M		negative
Bone marrow micronucleus assay— CF1 mouse, 8/dose	**Eugenol**, 100, 400, 600 mg/kg (intraperitoneal)		positive

Endpoint selection and indicated safety/uncertainty factors for congeneric group 18
Endpoint selection for acute-duration dermal exposure No relevant endpoints Endpoint selection for intermediate-duration dermal exposure NOAEL = 6000 ppm based on decreased body weights (6000 ppm × 0.1 diet conversion factor = 600 mg/kg bw/day) established in a 13-week rat dietary study Safety/uncertainty factors 10 intraspecies factor 10 interspecies factor 10 database uncertainties

Toxicology Table for Congeneric Group 31 (~13% of citronella)			
Study/Species / # of Animals per Group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
SUBCHRONIC TOXICITY STUDIES			
LIMONENE			
6-month oral (gavage)— Beagle dog; 5/sex/dose	***d*-Limonene:** 0, 100, 1000 mg/kg	NOEL = 100	↑ absolute and relative kidney weight at 1000 mg/kg
13-week gavage— F344/N rat, 10/sex/dose	***d*-Limonene:** 0, 150, 300, 600, 1200, 2400 mg/kg	NOAEL not set for males NOAEL = 600 (females)	≥150: dose related increase in severity for nephropathy in males only ≥600: decreased body weights (6, 12, 23 % lower than control for males in the 600, 1200, and 2400 mg/kg groups) ≥1200: rough hair coats, lethargy, excessive lacrimation 2400: death (5/10 males; 9/10 females) in first week; decreased body weight in females (11%)
13-week gavage— B6C3F1mice 10/sex/dose	***d*-Limonene:** 0, 125, 250, 500, 1000, 2000 mg/kg	NOAEL: 250	≥500: one female died ≥1000: rough hair coats, decreased activity, decreased body weight (10% at 1000 and 2000 mg/kg for males and 2% at 1000 and 2000 mg/kg for females) 2000: one male, two females died. Alveolar cell adenoma was observed in the lung of one female.
CHRONIC TOXICITY / ONCOGENICITY STUDIES			
***d*-LIMONENE** (published studies)			
2-year oral (gavage) oncogenicity—rat, 50/sex/dose	0, 75, 150 mg/kg (♂) 0, 300, 600 mg/kg (♀)	Males NOAEL not set Females NOAEL = 300	Male: ≥ 75 mg/kg: renal tubular cell hyperplasia, renal adenomas and adenocarcinomas Females: 600 mg/kg: survival significantly affected after week 39 **Evidence of carcinogenicity in male rats, but alpha-2 μ globulin-related and, therefore, of no biological relevance to humans**

Toxicology Table for Congeneric Group 31 (~13% of citronella)			
Study/Species / # of Animals per Group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
2-year oral (gavage) oncogenicity—B63CF$_1$ mouse, 50/sex/dose	0, 250, 500 mg/kg (♂) 0, 500, 1000 mg/kg (♀)	NOAEL = 250	No renal lesions or tumours in ♂ and ♀ Male: 250 mg/kg bw/day: survival significantly decreased (33/50, 24/50, 38/50 in control, low and high dose) 500 mg/kg bw/day: increased incidence of multinucleated hepatocytes (8/49, 4/36, 32/50 in control, low, high dose); Female: 1000 mg/kg bw: decreased body weight after week 28 (5–15%). **No evidence of carcinogenicity in mice**
REPRODUCTIVE AND DEVELOPMENTAL TOXICITY STUDIES			
α-TERPINENE (published studies)			
Oral (gavage) teratology study—Wistar rat, 15–28 sperm positive ♀/group	0, 30, 60, 125, 250 mg/kg/day on gestation days 6–15 98% pure	Maternal NOAEL = 60 Developmental NOAEL = 30	Maternal effects: ↓ weight gain at ≥ 125 mg/kg Developmental effects: delayed ossification of vertebral column and sternum, ↑ incidences of irregularly shaped os squamosum at ≥ 60 mg/kg; ↓ fetal weight at 250 mg/kg **Evidence of fetal sensitivity**
***d*-LIMONENE**			
Oral gavage—mice Developmental toxicity	0, 591, 2363 mg/kg bw days 7–12 of pregnancy	Maternal and Developmental NOAEL = 591	2363: significant decreases in body-weight gain in dams. Fetuses showed increased incidences of lumbar rib, fused rib, delayed ossification, and decreased body-weight gain.
β-MYRCENE			
Oral gavage—Wistar rat Developmental Toxicity	0.25, 0.5, 1.2 g/kg in corn oil days 6–15 of pregnancy	Maternal and Developmental NOAEL = 500	1.2 g/kg bw: decreased dam weightgain during first few days of treatment. One of 29 dams died. Increased incidence of fetal skeletal retardation and anomalies.
Oral gavage—Wistar rat Developmental/ Reproductive Toxicity	0.25, 0.5, 1.0, 1.5 g/kg in corn oil from day15 of pregnancy through parturiition, lactation until weaning	NOAEL = 250	≥0.5 g/kg: decreased birth weight, increased perinatal mortality and delayed developmental landmarks. ≥1.0 g/kg: fertility of female offspring impaired

Toxicology Table for Congeneric Group 31 (~13% of citronella)			
Study/Species / # of Animals per Group	**Dose Levels / Purity of Test Material**	**NOAEL (mg/kg bw/day)**	**Results/Effects**
GENOTOXICITY STUDIES			
***d*-LIMONENE**			
Ames Salmonella test; TA98, TA100, TA1535, TA137	0.3–3333 µg/plate ± S9		negative
Sister chromatid exchange test—Chinese hamster ovary cells	16.2–162 µg/mL ± S9		negative
Chromosomal aberration test—Chinese hamster ovary cells	10–100 µg/mL ± S9		negative
α-TERPINENE			
Ames Salmonella Test; TA97a, TA98, TA100, TA1535	NA ± S9		negative
β-MYRCENE			
Ames Salmonella Test; TA97a, TA98, TA100, TA1535	NA ± S9		negative

Endpoint selection and indicated safety/uncertainty factors for congeneric group 31

Endpoint selection for acute-duration dermal exposure

Developmental NOAEL = 30 mg/kg determined in a rat developmental toxicity study based on increased incidences of irregularly shaped os squamosum and os basisphenoid

Endpoint selection for intermediate-duration dermal exposure

Developmental NOAEL = 30 mg/kg determined in a rat developmental toxicity study based on increased incidences of irregularly shaped os squamosum; and delayed ossification of vertebral column and sternum

Safety/uncertainty factors

10 intraspecies factor
10 interspecies factor
3 fetal/offspring sensitivity

Table 3 Exposure Calculation by Congeneric Group for Adults and One Application of a Personal Insect Repellent Containing Citronella Oil Assuming 50% Dermal Absorption

Shaded cells do not exceed threshold values[5] for food exposure to that congeneric group (CG)				% Citronella oil			
				15	15	10	10
Congeneric group	Chemical group (structural class)	Toxicity class	Total % CG	Exposure[1] mg/kg/day	Exposure[3] mg/day	Exposure[2] mg/kg/day	Exposure[3] mg/day
1	Straight-chain primary aliphatic alcohols/aldehydes/acids, acetals and esters	I	0.1	0.495	0.347	0.0033	0.231
3	Alpha, beta- unsaturated (alkene or alkyne) straight-chain and branched-chain aliphatic primary alcohols/aldehydes/acids, acetals, and esters	I	28.3	1.401	98.06	0.934	65.373
4	Non-conjugated and accumulated unsaturated straight-chain and branched chain aliphatic primary alcohols/aldehydes/acids, acetals and esters	I	48.26	2.389	167.221	1.593	111.481
5	Saturated and unsaturated aliphatic secondary alcohols/ketones/ketals/esters with esters containing secondary alcohols	II	0.01	0.0005	0.0347	0.0003	0.0231
6	Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters containing tertiary alcohols	I	5.48	0.271	18.988	0.181	12.659
8	Secondary alicyclic saturated and unsaturated alcohols/ketones/ketals/esters	I	0.27	0.0134	0.936	0.00891	0.624
16	Aliphatic and alicyclic ethers	II	0.07	0.00347	0.243	0.00231	0.1617
18	Allylhydroxybenzenes	I (III)[4]	2.54	0.126	8.801	0.0838	5.867
31	Aliphatic and aromatic hydrocarbons	I	12.58	0.623	43.59	0.415	29.06
Total		I	97.53				
Total		II	0.08				
Total % of oil			97.61				

* Not previously reported in citronella oil

NA = not assigned

Toxicity classes[5] are:

I. 5th percentile NOEL mg/kg/day = 3.0; human exposure threshold (food uses) mg/day = (3 mg/kg bw/day / 70 kg bw) / 100 safety factor = 2.1 mg/day

II. 5th percentile NOEL mg/kg/day = 0.91; human exposure threshold (food uses) mg/day = 0.64 mg/day

III. 5th percentile NOEL mg/kg/day = 0.15; human exposure threshold (food uses) = 0.11 mg/day

Notes:

1. Derived as: (daily exposure of 9.9 mg/kg bw/day for 1 application of 15% citronella lotion) × % congeneric group × dermal absorption factor
2. Derived as: (daily exposure of 6.6 mg/kg bw/day for 1 application of 10% citronella lotion) × % congeneric group
3. Derived as: exposure at 15% citronella oil or at 10% citronella oil (mg/kg/day) × 70 kg bw = mg/day × [% component] × [100% or 50% dermal absorption]. Threshold is based on food exposure of these compounds when used as food flavourings.
4. In this congeneric group, methyl eugenol is in toxicity class III. However, this chemical is being treated separately in the risk assessment
5. Exposure thresholds published by Monro et al (1996) adjusted from assumed body weight of 60 kg to 70 kg.

Shaded cell does not exceed toxicity class exposure threshold value (i.e. acceptable)

Table 4 Margin of Exposure Calculation by Congeneric Group for Adults and One Application of a Personal Insect Repellent Containing Citronella Oil Assuming 50% Dermal Absorption

Shaded cells achieved necessary MOE (ie acceptable) for that congeneric group (CG)							% Citronella oil		
							15	15	15
CG	Chemical group (structural class)	Toxicity class	Total % CG	Acute NOAEL	Inter-mediate NOAEL	Safety Factor	Exposure[1] mg/kg/day	Acute MOE	Inter-mediate MOE
1	Straight-chain primary aliphatic alcohols/aldehydes/acids, acetals and esters	I	0.1	Risk assessment not necessary because exposure below threshold			0.00495	NA	NA
3	Alpha, beta- unsaturated (alkene or alkyne) straight-chain and branched-chain aliphatic primary alcohols/aldehydes/acids, acetals, and esters	I	28.3	60	60	100	1.401	43	43
4	Non-conjugated and accumulated unsaturated straight-chain and branched chain aliphatic primary alcohols/aldehydes/acids, acetals and esters	I	48.26	NA	100	1000	2.389	NA	42
5	Saturated and unsaturated aliphatic secondary alcohols/ketones/ketals/esters with esters containing secondary alcohols	II	0.01	Risk assessment not necessary because exposure below threshold			0.0005	NA	NA
6	Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters containing tertiary alcohols	I	5.48	250	250	1000	0.271	922	922
8	Secondary alicyclic saturated and unsaturated alcohols/ketones/ketals/esters	I	0.27	Risk assessment not necessary because exposure below threshold			0.0134	NA	NA
16	Aliphatic and alicyclic ethers	II	0.07	Risk assessment not necessary because exposure below threshold			0.00347	NA	NA
18	Allylhydroxybenzenes	I (III)[2]	2.54	NA	600	1000	0.126	NA	4772
31	Aliphatic and aromatic hydrocarbons	I	12.58	30	30	300	0.623	48	48
Total		I	97.53						
Total		II	0.08						
Total % of oil			97.61						

* Not previously reported in citronella oil

NA = not assigned

Toxicity classes and exposure thresholds are:

I. 5th percentile NOEL mg/kg/day = 3.0; human exposure threshold (food uses) mg/day = (3 mg/kg bw/day / 70 kg bw) / 100 safety factor = 2.1 mg/day

II. 5th percentile NOEL mg/kg/day = 0.91; human exposure threshold (food uses) mg/day = 0.64 mg/day

III. 5th percentile NOEL mg/kg/day = 0.15; human exposure threshold (food uses) = 0.11 mg/day

Notes:

1. Derived as: (daily exposure of 9.9 mg/kg bw/day for 1 application of 15% citronella lotion) × % congeneric group × dermal absorption factor.
2. In this congeneric group, methyl eugenol is in toxicity class III. However, this chemical is being treated separately in the risk assessment.

Shaded cell greater than necessary MOE (i.e. acceptable)

Table 5 Margin of Exposure Calculation by Congeneric Group for Adults and One Application of a Personal Insect Repellent Containing Citronella Oil Assuming 50% Dermal Absorption

Shaded cells achieved necessary MOE (ie acceptable) for that congeneric group (CG)							% Citronella Oil		
							10	10	10
CG	Chemical group (structural class)	Toxicity class	Total % CG	Acute NOAEL	Inter-mediate NOAEL	Safety Factor	Exposure[1] mg/kg/day	Acute MOE	Inter-mediate MOE
1	Straight-chain primary aliphatic alcohols/aldehydes/acids, acetals and esters	I	0.1	Risk assessment not necessary because exposure below threshold			0.0033	NA	NA
3	Alpha, beta- unsaturated (alkene or alkyne) straight-chain and branched-chain aliphatic primary alcohols/aldehydes/acids, acetals, and esters	I	28.3	60	60	100	0.934	64	64
4	Non-conjugated and accumulated unsaturated straight-chain and branched chain aliphatic primary alcohols/aldehydes/acids, acetals and esters	I	48.26	NA	100	1000	1.593	NA	63
5	Saturated and unsaturated aliphatic secondary alcohols/ketones/ketals/esters with esters containing secondary alcohols	II	0.01	Risk assessment not necessary because exposure below threshold			0.0003	NA	NA
6	Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters containing tertiary alcohols	I	5.48	250	250	1000	0.181	1382	1382
8	Secondary alicyclic saturated and unsaturated alcohols/ketones/ketals/ esters	I	0.27	Risk assessment not necessary because exposure below threshold			0.00891	NA	NA
16	Aliphatic and alicyclic ethers	II	0.07	Risk assessment not necessary because exposure below threshold			0.00231	NA	NA
18	Allylhydroxybenzenes	I (III)[2]	2.54	NA	600	1000	0.0838	NA	7158
31	Aliphatic and aromatic hydrocarbons	I	12.58	30	30	300	0.415	72	72
Total		I	97.53						
Total		II	0.08						
Total % of oil			97.61						

* Not previously reported in citronella oil

NA = not assigned

Toxicity classes and exposure thresholds are:

I. 5th percentile NOEL mg/kg/day = 3.0; human exposure threshold (food uses) mg/day = (3 mg/kg bw/day / 70 kg bw) / 100 safety factor = 2.1 mg/day

II. 5th percentile NOEL mg/kg/day = 0.91; human exposure threshold (food uses) mg/day = 0.64 mg/day

III. 5th percentile NOEL mg/kg/day = 0.15; human exposure threshold (food uses) = 0.11 mg/day

Notes:

1. Derived as: (daily exposure of 6.6 mg/kg bw/day for 1 application of 10% citronella lotion) × % congeneric group.
2. Exposure thresholds published by Monro et al (1996) adjusted from assumed body weight of 60 kg to 70 kg.

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